REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-15, 38, 39, 41, 48-52 and 67-71 are in the case.

I. CLAIM AMENDMENTS

Claims 16, 19 and 53 to 66 have been cancelled without prejudice to pursuing the canceled subject matter is a separate continuing case. New claim 70 is based on a combination of original claims 1 and 48, but with the time period being amended to 2 to 15 minutes based on page 17, line 29 and the range for C_{ther} of 0.8 to 5 ng/ml being based on the upper and lower limits at page 18, lines 4 and 3, respectively. New claim 71 is based on a combination of original claims 13 and 48, but with the time period being amended to 2 to 15 minutes based on page 17, line 29 and the range for C_{ther} of 0.8 to 5 ng/ml being based on the upper and lower limits at page 18, lines 4 and 3, respectively.

Claims 48 and 49 have been amended to specify that C_{ther} is 0.8 to 5 ng/ml rather than 0.8 to 2 ng/ml. Basis for an upper limit of 5 ng/ml appears at page 14, line 3. The word "analgesia" has been amended to read "analgesic" at line 2 of claim 48. In addition, "T_{main}" has been changed to "T_{maint}" in claims 51 and 52, and claim 68 has been amended to remove the term "or greater" at line 6.

The requested amendments do not constitute the introduction of new subject matter. Entry and favorable consideration of the requested changes are respectfully requested.

II. INFORMATION DISCLOSURE STATEMENT

Attention is directed to Verma *et al*, J. Psychol. Pharmacol., vol 7, no. 3, 270-275, 1993 and Soane *et al*, Int. J. Pharm., 178, 55-65, 1999. Copies of these documents are attached together with an Information Disclosure Statement. The abstract for JP 2000 229859 A has already been cited in an IDS previously filed in this application. Attached is a translation of this document. The Examiner's attention is also directed to the related cases US Application Serial No. 10/508,315 (now abandoned) and US Application Serial No. 11/798,384 (a continuation of the '315 application).

III. THE INVENTION

The present application is concerned with the provision of buprenorphine formulations for nasal administration (see page 3, lines 2 to 7 of the description). More particularly, the present invention provides aqueous solutions comprising buprenorphine and specific delivery agents and which solutions act to gel on the nasal mucosa. These solutions have been found to have an improved profile of absorption of buprenorphine into the systemic circulation. This is illustrated in Figure 1 of the present application which shows plasma concentration *vs.* time profiles for the administration of a buprenorphine/pectin formulation of the invention. As can be seen from the graph, the maximum plasma concentration of the drug is reached relatively quickly and the plasma concentration then decreases over an extended period.

The formulations of the invention thus combine rapid uptake of the buprenorphine across the nasal mucosa together with an increase in the residence time of the buprenorphine in the nasal cavity. They are therefore associated with both rapid onset of analgesia and prolonged analgesia. The claimed invention is not suggested by the cited art.

IV. THE OBVIOUSNESS REJECTIONS

(a) Claims 1-15, 38, 39, 41, 48-52 and 67-79 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Eriksen in view of Watts, Reich and Nairn. This rejection is respectfully traversed.

Claim 1 is directed to an aqueous solution suitable for intranasal administration comprising:

(1) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof;

(2) from 5 to 40 mg/ml of a pectin having a degree of esterification of less than 50%;

(3) which solution has a pH of 3 to 4.2, and is substantially free of divalent metal ions; and

(4) which gels on the nasal mucosa.

Such a formulation provides a relatively high plasma concentration a short time after administration, and the plasma concentration is well sustained. The claimed formulation is not suggested by the cited art.

Eriksen is concerned with nasal administration of buprenorphine. The solution administered comprises buprenorphine hydrochloride in dextrose and is adjusted to pH 5. This is to be contrasted with the present invention where the pH of the solutions is from 3 to 4.2. Moreover, as discussed below, a specific, unexpected advantage arises with formulations which have a pH from 3 to 4.2 which would not have been obvious to one of ordinary skill based on Eriksen, either taken alone or in combination with the cited secondary art.

Watts relates to a system for the delivery of drugs to mucosal surfaces such as the nose, the eye, the vagina, the rectum and the back of the throat. Watts provides compositions having a

sustained release (see, for example, page 2, line 23 to page 3, line 2, where it is stated: "*[i]t would be most beneficial ... for the drugs ... to have a long retention in the nasal cavity*" and page 4, lines 12 to 15, where it is stated: "*it would be advantageous to provide a single component liquid composition ... that gelled under the local environmental conditions to give good retention*".

Watts provides no indication that the disclosed formulations would provide a rapid uptake of the drug. In relation to systemic delivery, which the Examiner has recognised is of relevance to buprenorphine at page 14, line 16 of the Action, Watts states "*[c]ompositions of the invention may also be employed to control the plasma level versus time profile for readily absorbable drugs which are intended to act systemically (ie, to give a flatter profile)...[t]his can, for example, be of importance when side effects from high peak plasma levels are to be avoided*" (page 14, line, lines 13 to 18; emphasis added). The extent to which the absorption profile of a drug can be altered can be seen from Figure 2 of D2 which shows that for a fexofenadine/pectin formulation the release profile is almost entirely flat.

The Action states (page 14, line 9) that Watts teaches at page 3, lines 16 to 25 that incorporation of the pectins into nasal spray solutions "can be used to modify (increase or decrease) the absorption characteristics when administering drugs systemically or locally". The phrase "increase or decrease" is used in the Action to describe this modification, but such a phrase does not seem to appear in Watts. One of ordinary skill would glean from Watts that the absorption characteristics of the drug can be altered by use of a pectin and further (page 14, lines 13 to 18) that for systemically acting drugs, the absorption will be controlled *to give a flatter profile*. It is noteworthy that this passage in Watts says "ie. to give a flatter profile" and not "e.g to give a flatter profile", as this would lead the skilled person to understand that a flatter profile

will inevitably result when a pectin is used in conjunction with a systemically acting drug. Based on this, the skilled person would learn from Watts that the combination of a systemically acting drug with a pectin would result in a formulation with a flat profile which avoids high peak plasma levels. Thus, a skilled person looking to formulate a buprenorphine composition which combines rapid uptake of the drug with prolonged release would **not** consider Watts since Watts discloses that the resultant composition will have a flatter profile, and will not have the desired quick uptake.

Even if one of ordinary skill did consider combining Eriksen and Watts (it is believed this would not occur to one of ordinary skill), a composition of the present invention would not result or be rendered obvious thereby. In Eriksen, a buprenorphine hydrochloride/dextrose solution was initially prepared and then "the solution was adjusted to pH5" (page 803, column 2, line 11). Thus, the obtained solution was not of pH 5, but was instead specifically adjusted to this pH. According to Watts, page 16, line 29 to page 17, line 1, the pH of the compositions may be from 2 to 9, more preferably from 3 to 8 and most preferably from 4 to 7. The Action notes that Watts discloses at page 17, lines 3 to 6 that "the lower the DE of the pectin, the lower the pH at which the composition will gel". However, this does not disclose the use of lower pH's. Instead, it indicates that pectins with a lower DE can gel at lower pH. There is no disclosure that such pectins will only gel at low pH.

One of ordinary skill would understand a pH of 5 to be an important feature of Eriksen since the solution is specifically adjusted to achieve this. Furthermore, since this is within the most preferred range of Watts, the disclosures of both documents are consistent in this regard. Thus, the formulation resulting from a combination of these documents (if attempted) would have a pH of 5.

In contrast, the pH of the presently claimed solutions is lower, namely from 3 to 4.2. Thus, the formulations produced from a combination of Eriksen and Watts would **not** fall within the scope of the present claims. Furthermore, the lower pH range of 3 to 4.2 would not be obvious to one of ordinary skill because a specific unexpected advantage is exhibited by formulations having a pH from 3 to 4.2. Thus, as seen from Tables 3 and 3a on page 39 of the present application, solutions which have a pH within the range 3 to 4.2 specified in the present claims have an amount of buprenorphine detectable of between 12.3 and 15.8 mg/ml. When the pH is higher than this (values are provided for pH's of from 4.4 to 5.3), the amount of buprenorphine detected significantly falls. Therefore, the solubility of burpenorphine is much higher within the range specified in the present claims. This would not have been obvious to one of ordinary skill based on Eriksen and Watts or the other cited art. Thus, Nairn is cited for its apparent disclosure that nasal solutions are usually isotonic, and Reich is cited for its reference to the term "isotonic". These two references are otherwise irrelevant and do not give rise to a *prima facie* case of obviousness either alone or in combination with Eriksen and Watts.

Based on the above, it is clear that one of ordinary skill, as of the filing date of the present application, would not have been motivated to arrive at the presently claimed invention based on the cited art. In particular, the skilled person would not have considered Eriksen and Watts separately or together in seeking to produce a formulation which combines rapid release and sustained delivery of buprenorphine. Even if the cited references were combined, the resultant formulation would be disadvantageous compared to that presently claimed since it would have a higher pH. The present inventors have found that buprenorphine is less soluble in such higher pH solutions compared to those as claimed. Absent any motivation to combine the cited art, a *prima facie* case of obviousness has not been generated in this case. Withdrawal of

the obviousness rejection over Eriksen, Watts, Nairn and Reich is accordingly respectfully requested.

(b) Claims 16 and 53 to 59 and Claims 19 and 60 to 66

These claims have been cancelled by the present amendments. The obviousness rejections of these claims have therefore been rendered moot.

(c) New Claims 70 and 71

New claims 70 and 71 are based on claims 1 and 13, respectively, and further specify that on introduction into the nasal cavity of a patient to be treated, the buprenorphine or salt or ester thereof is delivered to the bloodstream to produce within 2 to 15 minutes a therapeutic plasma concentration C_{ther} of 0.8 to 5 ng/ml which is maintained for a duration T_{maint} of at least 2 hours. Thus, the fact that a relatively high plasma concentration is attained a short time after administration and that such a plasma concentration is well sustained are specifically defined as features of these claims.

New claims 70 and 71 are novel over the prior art for the same reasons as claim 1. In addition, the subject matter is patentable over the combination of Eriksen and Watts and the other cited secondary art for the same reasons as claim 1 which are explained in detail above. It is believed therefore that claims 70 and 71 are in condition for allowance along with the remaining claims in the case.

V. OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 13, 16, 38, 39, 41, 56 to 59 and 64 to 66 stand rejected on obviousness-type double patenting grounds over U.S. Patent 6,387,917 to Illum. This rejection is respectfully traversed.

Illum claims compositions for parenteral or non-parenteral administration of a systemically acting opioid analgesic in which a solubilising methanesulphonate anion enhances absorption of the drug. Thus, the Illum claims contain no suggestion of the formulations as presently claimed comprising from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 5 to 40 mg/ml of a pectin having a degree of esterification of less than 50%, which solution has a pH of from 3 to 4.2, is substantially free from divalent metal ions and gels on the nasal mucosa about formulations. Absent any suggestion in the claims of Illum of the features as claimed in the present case, there can be no obviousness-type double patenting. Withdrawal of the obviousness-type double patenting rejection is accordingly respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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